

REMARKS

A check for \$1085 for the fee for filing of a Request for Continued Examination (\$395), the fee for filing a supplemental Information Disclosure Statement (\$180) and the fee for a three-month extension of time (\$510) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A change in Power of Attorney and correspondence address previously has been filed.

Claims 1, 3-6 and 15-28 are pending. Claims 1 and 3-6 are amended and claims 15-28 are added herein. Claim 1 is amended to more distinctly claim the subject matter. Basis for the amendment of claim 1 is found throughout the specification (e.g., see original claim 1 as filed and page 3, line 7, through page 4, line 5). Claims 3-6 are amended to correct a minor formatting error.

Basis for added claim 15 is found throughout the specification (e.g., see page 10, line 21 through page 11, line 16). Basis for added claim 16 is found throughout the specification (e.g., see page 10, lines 8-11). Basis for added claims 17 and 24 is found throughout the specification (e.g., see page 4, lines 16-19 and page 12, lines 12-16). Basis for added claims 18, 25 and 26 is found throughout the specification (e.g., see page 11, line 24 through page 12, line 6). Basis for added claims 19 and 27 is found throughout the specification (e.g., see page 12, lines 6-11). Basis for added claim 20 is found throughout the specification (e.g., see page 3, line 7 through page 4, line 15, page 9, line 22 through page 10, line 20 and Fig. 1). Claim 28 recites the limitation, previously added by amendment to claim 1. No new matter is added.

THE REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

Claims 1 and 4-6 are rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Meier in view of Møller or the combination of Cheryan *et al.* in view of Møller or the combination of Meier or Cheryan *et al.* in view of Møller and Breslau *et al.* and the AMICON Brochure regarding Spiral-Wound/Hollow Fiber Systems (“AMICON”). The bases for rejection of the pending claims under 35 U.S.C. 103(a) are discussed in turn below.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited

references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

THE CLAIMS

Claim 1 is directed to a closed system for the continuous liquid phase modification and/or conjugation of proteins, purification and concentration thereof. The closed system includes an ultrafiltration concentration means, a reaction vessel fluidly connected to the ultrafiltration/concentration means, a backwash reservoir fluidly connected to the ultrafiltration/concentration means, and a pump fluidly interconnected between the ultrafiltration/concentration means and the reaction vessel. Claims 3-6 ultimately depend from claim 1 and are directed to various embodiments thereof. Independent claim 20 similarly recites that the system is closed and also requires that it is sterile.

1. Meier in view of Møller

Claims 1, 3, 5 and 6 are rejected under 35 U.S.C. §103(a) over Meier (US 5,262,053) in view of Møller (US 5,620,605) because Meier allegedly teaches every element of the claimed system except a backwash reservoir, but Møller allegedly cures this deficiency. This rejection respectfully is traversed.

TEACHINGS OF THE CITED ART

Meier (U.S. 5,262,053)

Meier teaches that tanning agents and proteins are not sufficiently removable from some liquids, such as beer and fruit juice, by a filter but are removable by adsorption to a granular stabilizer. Meier teaches a system for filtering and stabilizing a liquid medium, such as beer or juice, that contains a tanning agent and/or proteins. Meier teaches that the system includes a cross-flow filter in the ultrafiltration or microfiltration range, a working tank, a filtrate tank and a metering container. Meier teaches that during cross-flow membrane filtration, the unfiltered medium is continuously kept in circulation by pumping and a stabilizer from the metering container is continuously metered into the unfiltered medium in the working tank. Meier teaches that the system includes a feed line (18) through which water or a cleaning liquid, such as a lye or acid, can be introduced into the filter to clean and regenerate the stabilizer (*e.g.*, PVPP). Meier does not teach a closed system.

Møller (U.S. 5,620,605)

Møller teaches a cassette membrane system for use in low pressure separations. Møller teaches that its membrane fluid separation apparatus includes at least one cassette having a plurality of membranes and a support for supporting the membranes at their peripheral edges, where the membranes are in the form of a plurality of membrane layers, each layer is sealed at at least two of its peripheral edges to one or more adjacent membrane layer(s), such that the membranes define a feed side and a permeate side, where the permeate side of each of the membranes opens into at least one collection area, and where the membranes are sealed such that the feed side and permeate side of the membranes do not communicate otherwise than through the membranes. The system of Møller also includes a means for contacting the feed fluid with the feed side of the membranes, a means for removing the permeate from the permeate collection chamber, and a means for creating a transmembrane pressure differential by reducing the pressure on the permeate side of the membranes to subatmospheric pressure. Møller teaches that its system includes a back-wash tank (18) to hold fluid to be used to back-wash the membrane cassettes (col. 13, lines 29-31). Møller teaches that FIGS. 5, 6 and 7 illustrate three different views of its open separation system (see col. 5, lines 2-4).

ANALYSIS

It respectfully is submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Meier with the teachings of Møller does not result in the instantly claimed systems.

The instant claims are directed to closed systems for performing a reaction, where the system includes an ultrafiltration concentration means, a reaction vessel fluidly connected to the ultrafiltration/concentration means, a back-wash reservoir fluidly connected to the ultrafiltration/concentration means, and a pump fluidly interconnected between the ultrafiltration/concentration means and the reaction vessel. The system as claimed, which combines the reaction and purification steps in a single system, is a closed system.

Meier does not teach or suggest a system that includes a back-flush reservoir nor does Meier teach or suggest a closed system nor a system in which the reaction and purification steps are performed. The system taught by Meier is an open system. For example, Meier teaches that water or cleaning liquids are introduced into its filtration installation from outside the system via the feedline 18. There is no teaching or suggestion in Meier that its filtration installation is a closed system. Further, Meier teaches that its retentate, which includes slurry substances such as yeast, is unwanted material that is removed from the system and destroyed by treating with lye or acid (see col. 6, lines 2-15). Thus, there is no suggestion for modification of Meier to produce a closed system, since the retentate in the methods described in Meier is **discarded**. Meier does not teach or suggest a sterile system.

Møller does not teach or suggest the elements missing from the teaching of Meier. Møller does not teach or suggest a closed system in which reaction and purification steps are performed. For example, Møller teaches its system is an open separation system, and that FIGS. 5, 6 and 7 illustrate three different views of its open separation system (see col. 5, lines 2-4). Thus, Møller teaches that its separation system is an open system. Møller does not teach or suggest a sterile system.

Therefore, the combination of teachings of Meier and Møller fails to teach or suggest and does not result in the instantly claimed systems. Neither Meier nor Møller, alone or in combination, teaches or suggests a closed system nor does the combination teach or suggest a system in which the reaction and purification steps are performed in the same closed system. In addition, the combination of Meier and Møller fails to teach or suggest and does not result in the instantly claimed closed systems that are sterile. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

2. Cheryan *et al.* in view of Møller

Claims 1, 5 and 6 are rejected under 35 U.S.C. §103(a) over Cheryan *et al.* (US 4,443,540) in view of Møller (US 5,620,605) because Cheryan *et al.* allegedly teaches every element of the claimed system except a backwash reservoir, but Møller allegedly cures this deficiency. This rejection respectfully is traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

TEACHINGS OF THE CITED ART

Cheryan *et al.* (U.S. 4,443,540)

Cheryan *et al.* teaches a process that can be operated in a continuous manner for the preparation of protein hydrolyzate. Cheryan *et al.* describes an **open** system that includes a hollow fiber membrane filtration zone, a protein holding tank, an enzyme holding tank and a protein hydrolysis reactor. Cheryan *et al.* teaches that partially hydrolyzed protein solution is withdrawn from the hydrolysis reactor using a pump and the solution is introduced into the hollow-fiber membrane filtration zone, where insufficiently hydrolyzed protein is rejected by the membrane filter and returned to the hydrolysis reactor. Cheryan *et al.* teaches that the permeate containing the hydrolyzed protein is collected in a collection means. Cheryan *et al.* teaches that its process eliminates the prior art need to back-wash the membranes because there is no deposition of solids at the membrane surface, thus minimizing concentration polarization and fouling effects (col. 7, lines 1-9). Cheryan *et al.* teaches that its slurry is centrifuged or pre-filtered before ultrafiltration (col. 5, lines 3-6).

Cheryan *et al.* teaches that its continuous process in combination with the activity of the enzyme used and the composition in its hydrolysis reactor **eliminates** the need to backwash the membranes in its system because there is no deposition of solids at the membrane surface and that this minimizes concentration polarization and fouling effects. Thus, Cheryan *et al.* teaches that its process eliminates the prior art need to back-wash the membranes. Hence, Cheryan *et al.* provides no teaching or suggestion of a system that includes a back-flush reservoir. Further, as noted, Cheryan *et al.* does not teach or suggest a closed system.

Møller (U.S. 5,620,605)

See discussion above. As noted, Møller fails to teach or suggest a closed system.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Cheryan *et al.* with the teachings of Møller does not result in the instantly claimed systems.

Neither Cheryan *et al.* nor Møller, singly nor in any combination thereof, teaches every element of the claimed subject matter. As discussed above, the instant claims are directed to closed systems for performing a reaction, where the system includes an ultrafiltration concentration means, a reaction vessel fluidly connected to the ultrafiltration/concentration means, a back-wash reservoir fluidly connected to the ultrafiltration/concentration means, and a pump fluidly interconnected between the ultrafiltration/concentration means and the reaction vessel. Cheryan *et al.* teaches its system is designed to eliminate the need for a back-flush reservoir. One of the elements of the instantly claimed system is that it is a closed system. As noted, Cheryan *et al.* teaches an open system. Cheryan *et al.* fails to teach or suggest a closed system.

Møller does not teach or suggest the elements missing from the teaching of Cheryan *et al.* For example, Møller does not teach or suggest a closed system. Møller teaches that its system is a large open separation system, and that FIGS. 5, 6 and 7 illustrate three different views of its open separation system (see col. 5, lines 2-4). Thus, Møller teaches that its separation system is an open system. Furthermore, since Cheryan *et al.* teaches that its system is designed to eliminate the need for a back-flush reservoir, combining its teachings with those of Møller would not have led one of ordinary skill in the art to have added a back-flush reservoir to the system of Cheryan *et al.* since such would have defeated the purpose of the system taught by Cheryan *et al.*

Thus, the Cheryan *et al.* and Møller, alone or in any combination, fails to teach or suggests a system that includes all of the elements as claimed. The combination fails to teach an open system, and also fails to teach or suggest an open system that includes a back-flush reservoir. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

3. Combination of Meier, Møller, Breslau *et al.* and AMICON or Cheryan *et al.* Møller, Breslau *et al.* and AMICON

Claim 4 is rejected under 35 U.S.C. §103(a) over Meier in view of Møller, Breslau *et al.* (U.S. 4,986,918) and AMICON or Cheryan *et al.* (US 4,443,540) in view of Møller, Breslau *et al.* (U.S. 4,986,918) and AMICON because the combination of Meier and Møller or Cheryan

et al. and Møller teaches every element of the claimed system except a spiral diafiltration cartridge as the ultrafiltration means, but allegedly the combination of the teachings of Breslau *et al.* and AMICON cures this deficiency. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 4 depends from claim 1 (discussed above) and includes every element thereof.

TEACHINGS OF THE CITED ART

Meier (U.S. 5,262,053)

See related section above.

Cheryan *et al.* (U.S. 4,443,540)

See related section above.

Møller (U.S. 5,620,605)

See related section above.

Breslau *et al.* (U.S. 4,986,918)

Breslau *et al.* teaches a separation system capable of operating in many of the modes of operation of a separation system, including suction backwash, while keeping the filtrate stream separate from the process stream. Breslau *et al.* teaches that the operating modes for a separation system include (a) normal flow of the process side fluid during filtration; (b) reverse flow of the process side fluid during filtration; (c) normal flow of the process side fluid during filtration with filtrate recycle; (d) reverse flow of the process side fluid during filtration with filtrate recycle; (e) suction backwash with the backwash liquor exiting the process side flow channels simultaneously in the normal flow and reverse flow directions; (f) suction backwash with the backwash liquor exiting the process side flow channel in the normal flow direction; (g) suction backwash with the backwash liquor exiting the process side flow channel in the reverse flow direction. Breslau *et al.* teaches that its membrane separation places a process pump within a network of valved conduits forming a conduit loop connected in such a manner as to allow the system to be used for all these operating filtration modes while keeping the filtrate stream completely separate from the feed stream. Breslau *et al.* teaches that the membranes used in ultrafiltration may be of various configurations such as hollow fiber, flat sheet, spiral wound or tubular, and that hollow fiber polymeric membranes are employed in its separation system. The system described in the reference includes a valved conduit loop, a process fluid tank, a separation module and a pump. The system is open.

AMICON Brochure: Operating Principles of Ultrafiltration Systems

AMICON teaches principles of ultrafiltration and flow schematics for concentration and diafiltration. AMICON teaches hollow fiber concentrators and spiral-wound/hollow fiber concentrators. AMICON teaches that good fluid velocity minimizes concentration polarization and thus minimizes build-up of retained solutes at the membrane surface.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

a. The combination of the teachings of Meier and Møller with the teachings of Breslau *et al.* and AMICON does not result in the instantly claimed systems.

As discussed above, the combination of the teachings of Meier and Møller does not teach or suggest every element of claim 1. Claim 4 includes every element of claim 1. Thus, the combination of Meier and Møller does not result in the system of claim 4.

Applicant respectfully submits that neither Breslau *et al.* nor AMICON remedies the defects in the combination of the teachings of Meier and Møller. For example, Breslau *et al.* does not teach or suggest a closed system. There is no discussion regarding a closed system in Breslau *et al.* The Figures of Breslau *et al.* illustrate process tank T1 as being open. Thus, even if Breslau *et al.* teaches that the membranes used in ultrafiltration can be of various configurations such as hollow fiber, flat sheet, spiral wound or tubular, the teachings of Breslau *et al.* does not teach or suggest the elements missing from the combination of the teachings of Meier and Møller, such as the system being a closed system.

AMICON does not cure these defects. AMICON teaches hollow fiber concentrators and spiral-wound hollow fiber cartridge concentrators. AMICON teaches that good fluid velocity minimizes concentration polarization and thus minimizes build-up of retained solutes at the membrane surface. Reduced build-up of retained solutes at the membrane would result in minimizing the need to back-flush the membranes. AMICON does not teach or suggest the system as instantly claimed, which combines a reaction vessel and a purification means, such as an ultrafiltration/concentration in a single closed system.

Applicant respectfully submits that none of Meier, Møller, Breslau *et al.* or AMICON, alone or in any combination, teaches or suggests a system that includes all of the elements set forth in claim 4. Thus, the combination of the teachings of Meier *et al.* and Møller and Breslau *et al.* and AMICON does not render the claimed subject matter obvious. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

b. The combination of the teachings of Cheryan *et al.* and Møller with the teachings of Breslau *et al.* and AMICON does not result in the instantly claimed systems.

As discussed above, the combination of the teachings of Cheryan *et al.* and Møller does not teach or suggest every element of claim 1. Claim 4 includes every element of claim 1. Thus, the combination of Cheryan *et al.* and Møller does not result in the system of claim 4.

Applicant respectfully submits that neither Breslau *et al.* nor AMICON remedies the defects in the combination of the teachings of Cheryan *et al.* and Møller. For example, Breslau *et al.* does not teach or suggest a closed system. There is no discussion regarding a closed system in Breslau *et al.* The Figures of Breslau *et al.* illustrate process tank T1 as being open. Thus, even if Breslau *et al.* teaches that hollow fiber or spiral wound membranes are used in ultrafiltration, Breslau *et al.* does not teach or suggest the elements missing from the combination of the teachings of Cheryan *et al.* and Møller, such as the system being a closed system.

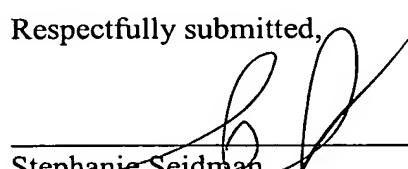
AMICON does not cure these defects. AMICON teaches hollow fiber concentrators and spiral-wound hollow fiber cartridge concentrators. AMICON teaches minimizing retained solute buildup at the membrane by fluid velocity. AMICON does not teach or suggest the system as instantly claimed, which combines the reaction and purification steps in a single closed system.

Applicant respectfully submits that none of Cheryan *et al.*, Møller, Breslau *et al.* or AMICON, alone or in combination, teaches or suggests a system that includes all of the elements set forth in claim 4. Thus, the combination of the teachings of Cheryan *et al.* and Møller and Breslau *et al.* and AMICON does not render the claimed subject matter obvious. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,


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